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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/662,649	09/14/2000	Zaid Jayyosi	02481.1690	1144

5487 7590 02/06/2002

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EXAMINER
PATEL, SUDHAKER B

ART UNIT	PAPER NUMBER
1624	12

DATE MAILED: 02/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/662,649	Zaid Jayyosi et al
Examiner	**Art Unit**
Sudhaker Patel	1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Jan 22, 2002

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-37, 47, 48, 53-59, 61-66, 70, and 91-101 is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-37, 47, 48, 53-59, 61-66, 70, and 91-101 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Applicants' communication paper # 11 dated 1/22/02 is acknowledged.

It is noted that this application is continuation of international application no. PCT/USOO/11833 filed 44/28/2000.

As applicants are aware this application as filed had originally claims 1-90(pages 124-159), and a lengthy 3 pages(pages 160-162) abstract.

Wide various amendments, applicants have canceled claims 38-46,49-52,60,67-69,71-90, amended claims 1,16,24,30,31,33,34,36, and added new claims 91-101, with additional generic Formula as recited in claim 97.

Under the restriction/election as required by Office Action paper #6 dated 6/601 applicants had opted to elect the floating Group XII and provided the generic nature of variables Ar I, Ar II, A, B, E,Z, R1-R8.

This election of Group XII consisted of:

Applicants' election of the subject matter with traverse of Group XII, claims(in part) 1-2,8,15,26-31,47-48,53-59,61-66,91-92,96, drawn to compounds, corresponding compositions, a method of use of generic Formula (I) wherein Ar I (Heterocycle optionally substituted);Ar II (= phenyl, optionally substituted); A (= -0(C(R15)(R16))g-0-;B/E(= a chemical bond); Z (= non-heterocycle);c/d(= zero);R1-R4 (= independently H, Halogen or alkyl); and the species of the compound of Example 51 cited on page 95 lines 12-17 of the specification(= 2-methyl-6-(3-(2-phenyl-oxazol-4-ylmethoxy)-propoxymethyl)-benzoic acid).Since claims 1-2,8,15,26-31,47-

48,53-59,61-66,91-92,96, link with other inventions they would be examined bearing in mind the subject matter as elected by the applicants only. Applicants are urged to cancel the non-elected claims and also limit the scope of the claims to the subject matter as elected in reply to this Office Action. Claims 3-7,9-14,16-25,32-46,49-52,60,67-90,93,94,96 would not be considered as they constitute non-elected invention, 37 CFR 1.142(b).

All that applicants have tried to accomplish is to add new claims and amend claims 1, 55 wide their amendment paper # 11 as recited above.

Applicants' cancellation, amendments, and addition of new claims together with arguments have been considered but not found persuasive for considering the application to be examined as a single piece.

Based on the remarks and above facts, the rejections made under 35 U.S.C. 103(a) are now withdrawn. Applicants' amendments for Z = -COOH only vs. Ref.'510 which claims Z = heterocycle(=tetrazole) has avoided the art rejection. The other reference ' 188 disclosed quinolinyl ethers, and present amendments to various groups, namely Z, B, E, c, d, the same has been avoided by the applicants.

However, upon further consideration and review the rejections made under 35 U.S.C. 112 are maintained further together with following remarks.

1). The claims have not been limited to A = -0(C(R15)(R16))g-0-. Note claim 8 does not belong to elected group because it is a different variable for A. Deletion where necessary to maintain the variable A = -0(C(R15)(R16))g-0-. is requested.

2). The claims as presented now does not limit the scope of Ar II (= phenyl, optionally substituted) e.g claim 54 is dependent on generic claim 1.

3). Claim 33 does not limit Z component to non-heterocycle and is dependent on generic claim 1.

4). Specification is not enabling for claim 25 which absent and missing altogether.

5).Claims 47-52 which are recited on pages 137-155 presenting various structures are still not thoroughly cleaned up for the unwanted citation of ions e.g. CL, or temperature figures expressed in Celsius, words like (dec), see page 144 specifically lines 3-5 and others where applicable.

6).As regard to question of what has been examined and considered, the examiner has searched the components Z = nonheterocycle only; Ar I = Pyridine, Quinoline, partially or fully hydrogenated, piperidine, 2-substituted-oxazole, other 5-membered heterocycle involving 1 N, and 1 or more of other heteroatoms only.

Additional search involving heterocyclkes both for Z and AR I components will involve undue burden to the examiner because 6 -membered pyrimidine or 1,4-diazine or 1,2 diazine will involve class 544; Thiophene, furan and pyrane, or 1,3 dioxane, 1.4-dioxane will fall in class 549, and totally no-heterocyclic molecules as recited e.g on page 145 will fall in classes 564, 558, 560, 568. This when considered the utility class of 514, will generate additional many subclasses which is multiple search areas in the limited time available to the examiner.

Based on above facts the earlier rejections made under 35 U.S.C. 112 are not withdrawn. Following additional remarks and grounds for not considering the application for allowance at this stage apply.

The claim(s) as presented include monomeric, polymeric or a single molecule of a heterocycle(s) or aromatic hydrocarbon(s) including(but not limited to) mono-, bi-, tri-, polycyclic nuclei. This situation when coupled with other terms and definitions, and integers will generate only theoretically possible/impossible structures. Applicants are requiring(the public) the reader to think of the specific compound that applicants may have intended. However, the claim language as presented does not tell the reader what exactly is being claimed. Therefore, it does not comply with 35 U.S.C. 112, 2nd paragraph. It would require undue experimentation on the part of the reader to determine which (non)heterocyclic rings are producible and makes him(reader) co-inventor. Applicants are expected, in return for the patent grant for 17/20 years, a specific fact disclosure. Many of the combinations claimed have not been made yet. What is the source of the starting materials? Conception of what the intended (non)heterocyclic ring, may be, should not be left to the reader. Where is, what is intended by the applicants, supported in the specification with sufficient representative exemplification? Note United Carbon Co. V.s. Binney & Smith Co. 55 USPQ 381; Supreme court of the United States (1942) " AN INVENTION MUST BE CAPABLE OF ACCURATE DEFINITION, AND IT MUST BE ACCURATELY DEFINED TO BE PATENTABLE", ABOVE AT 386.

The written description is considered inadequate here in the specification. Conception should not be role of the reader. Applicants, should, in return for 17/20 year monopoly, be disclosing to the public that which they know as an actual demonstrated fact. This is a 35 U.S.C. 112, first and second paragraph rejection. If the public find that it works, the applicants claim it is

not a proper basis for patentability; In re Kirt, 153 USPQ; at page 53.Furthermore, due to the unpredictability in the pharmaceutical art, applicants are required to demonstrate that all the embodiment claimed(compound, its pharmaceutically acceptable salts, -N-oxides, hydrates or solvates thereof) posses the claimed utility and not merely for further investigation or research. See In re Fisher, 166 USPQ 18. A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention of its filing date, In re Glass 492 F 2d 1228; 181 USPQ 31 (CCPA 1974).

7).SCOPE OF ENABLEMENT FOR METHODS: Scope of making and using composition(s) for treating a generic patient suffering from generically claimed physiological disorder(s) capable of being modulated by a generic compound having PPAR ligand binding related to both as ***agonistic*** as well as ***antagonistic*** activity, is not enabled.

Pages 1-4,118-123 describe various prior arts/assays describing uses of various compounds in relation to determination of activity related to PPAR receptor(s) but specifically fail to provide any pertinent data related to instant compounds for the reader(examiner) to visualize the utility. See Brenner v. Manson, 148 USPQ 689 which requires that utility be developed up to a point where "specific benefits exist in currently available form". The tests and assays as provided by the applicants can not possibly meet such a standard. Note Bindra v.s.. Kelly 206 USPQ 570, where, if "actual testing" is not done (and here, it is not) then one must establish "such facts as would be convincing that such utility could be foretold with certainty".

The screening test isn't designed to demonstrate "practical utility". It is designed to determine which compounds ought to be tested for actual utility.

For additional discussion of the limitations of the usefulness of screening testing, and the standards for using these to meet the requirements of 35 U.S.C. 112 para 1 see

Ex parte Busse 1 USPQ 2nd 1908

Hoffman v.Klaus 9 USPQ 2nd 1657

Ex parte Balzarini, 21 USPQ 2nd 1892

Ex parte Maas, 14 USPQ 2nd 1762.

For the burden on applicants when there is reasonable doubt, see Ex parte Jovanovics, 211 USPQ 907; Isenstead v. Watson 115 USPQ 408, 410 and Ex parte Krepelka 231 USPQ 746.

Applicants' attention is also drawn to fact that the development path for a laboratory compound to medicine as a "pharmaceutical composition" is an accepted very difficult and complicated process, and the reader(examiner) is left to visualize the merits of the animal model testing to be converted into a utility for mammals including humans without actually testing on human.

Together with this when one considers the toxicity/tolerance/efficacy/effectiveness aspect for human, it is very confusing to read the same from the claims as they are presented. The instant application has composition claims 53 as well as 70 and a total of 13 method claims(= 54-66) which is not a single method of use. Particular attention is called to Ex parte Busse 1 USPQ

2nd 1908, which had testing no less impressive than here, and on a claim with just a single species. Yet the claim was refused.

Claims are rejected, 35 U.S.C. 112 para. 1 and 35 U.S.C. 101 as lacking enablement for the alleged utility.

The examiner has the authority to require substantiation when utility is "sufficiently unusual" (Ex parte Krepelka, 231 USPQ 746) and reject if it is not provided(In re Ruskin, 148 USPQ 221; Ex parte Jovanovics, 211 USPQ 907, 909; In re Novak, 1345 USPQ 335). Note also Isenstead v. Watson 115 USPQ 408, 410.

Several cases have been defined what enabling utility requires:

Brenner v. Manson, 148 USPQ 689 requires that utility be developed to a point where "specific benefits exists in currently available form". Similar is the "immediate benefit to the public" standard that Nelson v. Bowler 206 USPQ 880 refers to. In re Hartop, 135 USPQ 419 is " whether the invention has been brought to such perfection as to be capable of practical employment". This language is echoed in Bindra vs. Kelly, 206 USPQ 570, 575:

"Probable utility does not establish practical utility. Practical utility can...be established only by actual testing therefore or by establishing such facts as would be convincing that such utility could be foretold with certainty".

What applicant has in this case is at best just a promising lead, which will not meet the required standards for testing/evaluation of the compounds. What applicant has in this case is at

best just a promising lead, which will not meet the above standard. Note In re Gangradharam, 13 USPQ 2nd 1568.

This case contains no testing but might in the future. The question of what standard testing needs to meet has been addressed a number of times. For example, in Hoffman v. Klaus 9 USPQ 2nd, 1657, 1660.

No"evidence" for a "correlation" exists in this case.

A similar case was Knapp vs. Anderson, 177 USPQ 688,691, where the Court referred to " The lack of correlation between the bench test and actual service conditions...". The test was described as being "preliminary in nature, serving only to screen out the most unlikely candidates, and thereby limiting the need for more expensive but reliable engine tests". A fairly similar situation pertains here.

In Ex parte Aggarwal, 23 USPQ 2nd 1334, 1338 it was stated:

"The in vitro and in vivo test conducted by appellants have not been shown to have been recognized by the art as predictive of success with lumphotoxin in the treatment of tumors".

But the burden remains on applicant to show this. In re Hozumi, 226 USPQ 353 says that applicants must clearly show a "nexus between the test results... and a predictability of success".

For more general requirement of compliance with 35 U.S.C. 112 para 1. See In re Argoudelis, 168 USPQ 99,104:

"It is essential that there be no question that, at the time an application for patent is filed... no technological problems, the resolution of which would require more than ordinary skill and reasonable time, remain in order to obtain an operative, useful embodiment".

MPEP 806.05(h) provides for one method of use to be examined with the elected compounds. A broad disclosure of utility as in the cited claims can not be deemed in compliance with 35 U.S.C. 112, first paragraph.

This requirement of one specific utility is also in compliance with 37 CFR 1.475 the unity of Invention Practice in International Applications and National Phase Applications under U.S.C. 371, and PCT Rule 13.2.

Therefore, applicants should limit the method claim to a sole "specific utility".

Statements of utility which relate to or imply treatment of a disease(s) related to physiological disorders(s) to be modulated by PPAR ligand binding activity are subject to closer scrutiny. Ex parte Moore et al.(POBA 1960) 128 USPQ 8. Claims do not meet the Utility Guidelines. The claims do not qualify as one utility statement, and are not believable on their face. Claims require too much experimentation to determine what patient dosage relationship would produce what results. It is not believable on its face that any one compound would have all of those utilities. In re Hozumi, 226 USPQ 353.

The quantity of experimentation need would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a single compound for a method of treating any and all physiological disorder(s)/disease(s) including but not limited to diabetes, Syndrome X, cardiovascular condition and other diseases/conditions involving both activities not only as agonistic but also as antagonistic is unbelievable on the face of it. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech v.s. Novo Nordisk*, 42 USPQ 2nd

A disclosure involving a new chemical compound or composition must teach persons skilled in the art how to make the compound or composition. See MPEP 608.01 p 600-64.There is no reasonable correlation between narrow disclosure in applicants' specification and broad scope of protection sought in the claims, In re Vaeck 20 USPQ 2d 1438.

As the search and examination has been limited to Group XII invention with above limitations, any additional efforts to search would constitute undue burden involving more time. However, compounds claims 1-37,47-48 91-95,978-101 if presented as claiming elected invention of Group XII after resolving various issues as outlined above would be considered for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker Patel, D.Sc.Tech. whose telephone number is (703) 308 4709.

The examiner can normally be reached on Monday thru' Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by the phone are unsuccessful, the examiner's supervisor, Dr.Mukund Shah can be reached at (703) 308 4716.

A facsimile center has been established for Group 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or (703) 305-3592.

Any inquiry of general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

Mukund J. Shah

Mukund Shah

sp

Supervisory Patent Examiner

February 3, 2002.

Art Unit 1624